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Venous thromboembolism during combat operations: a 10-y review

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ABSTRACT

Background: This article examines the incidence of venous thromboembolism (VTE) in combat wounded, identifies risk factors for pulmonary embolism (PE), and compares the rate of PE in combat with previously reported civilian data.
Methods: A retrospective review was performed of all U.S. military combat casualties in Operation Enduring Freedom and Operation Iraqi Freedom with a VTE recorded in the Department of Defense Trauma Registry from September 2001 to July 2011. The Military Amputation Database of all U.S. military amputations during the same 10 y period was also reviewed. Demographic data, injury characteristics, and outcomes were evaluated.
Results: Among 26,634 subjects, 587 (2.2%) had a VTE. This number included 270 subjects (1.0%) with deep venous thrombosis (DVT), 223 (0.8%) with PE, and 94 (0.4%) with both DVT and PE. Lower extremity amputation was independently associated with PE (odds ratio [OR], 1.70; 95% confidence interval [CI], 1.07 2.69). A total of 1003 subjects suffered a lower ex tremity amputation, with 174 (17%) having a VTE. Of these, 75 subjects (7.5%) were having DVT, 70 (7.0%) were having PE, and 29 (2.9%) were found to have both a DVT and a PE. Risk factors found to be independently associated with VTE in amputees were multiple ampu tations (OR, 2; 95% CI, 1.35 3.42) and above the knee amputation (OR, 2.11; 95% CI, 1.3 3.32).
Conclusions: Combat wounded are at a high risk for thromboembolic complications with the highest risk associated with multiple or above the knee amputations.

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1. Introduction

Tissue injury in conjunction with both the inflammatory response and the delayed inhibition of fibrinolysis places the trauma patient at increased risk for venous thromboembolic events, which are major sources of morbidity and mortality in this population [1]. In fact, after surviving the first 24 h, pulmonary embolism (PE) is the third most common cause of death after trauma [2–5]. The incidence of venous thromboembolism (VTE), which include deep venous throm bosis (DVT) and PE in hospitalized trauma patients, ranges from less than 1%–58% depending on the population studied, detection methods (i.e., venography, color flow Doppler, and spiral computer tomography), prophylactic anticoagulation strategies used, and other factors [2–13]. This variability be tween studies makes it difficult to assess the risk of VTE for an individual patient and apply treatment strategies to optimize care. This is particularly true for combat casualties, which

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have different and oftentimes more severe injuries, require longer transportation times with extended immobilization, and frequently cannot receive pharmacologic prophylaxis of VTE because of the risk of bleeding. The purpose of this study was to determine the incidence of VTEs among combat casualties injured during wartime to better predict those patients who are at increased risk of VTE (DVT and PE). Additionally, we hypothesized that (1) the incidence of VTE in combat wounded is higher than in civilian trauma, and (2) the risk factors for VTE between military and civilian cohorts are different.

2. Methods

This retrospective study was conducted under a protocol approved by the San Antonio Military Medical Center Institutional Review Board. The Department of Defense Trauma Registry (DoDTR) (Fort Sam Houston, TX), formerly known as the Joint Theater Trauma Registry, was queried for data on United States military service members who were injured during Operation Enduring Freedom (OEF) or Operation Iraqi Freedom (OIF) and sustained a VTE (DVT and PE) from September 2001 through July 2011. This includes all VTEs identified at level III (Combat Support Hospital in theater of war), level IV (Landstuhl Regional Medical Center [LRMC], regional evacuation center in Landstuhl, Germany), and level V (participating military tertiary care centers within the United States). Patients reported as killed in action or dead on arrival were excluded from analysis. Patients with VTEs were identified using *International Classification of Disease*, ninth edition, and Abbreviated Injury Scale (AIS) 2005 injury codes. Complications at all facilities were identified using *International Classification of Disease*, ninth edition codes. The dominant injury mechanism was categorized as explosive device, gunshot wound, motor vehicle accident, helicopter crash, or machinery and equipment. Injury Severity Score (ISS), AIS, injury date, and complications when in theater were collected from the DoDTR.

2.1. *Data analysis*

A list of VTE risk factors was assembled by military doctors with experience with VTE during OEF and OIF and included previously identified risk factors from civilian trauma studies [2,12]. For each risk factor, subjects with a DVT were compared against those patients with a PE and an odds ratio was calculated. Once a lower extremity amputation was identified as the risk factor for PE, then demographics, injury characteristic, and amputation level were collected from the Military Amputation Database (MAD) (Extremity Trauma and Amputation Center of Excellence, Fort Sam Houston, TX). The MAD contains demographic information on all United States military personnel who underwent amputations between October 1, 2001 and July 30, 2011. MAD is not specific to any service branch or treatment facility and defines a major extremity amputation as an amputation proximal to the carpal or tarsal bones of a limb [14]. The following data were extracted from the MAD for each service member suffering an amputation: age at injury, date of injury, date of first amputation, amputation level, and a brief narrative history of the injuring event and acute medical care provided. Additional information pertaining to the injury and treatment of each amputee was obtained from the DoDTR.

2.2. *Statistical analysis*

Variables for the univariate analysis were identified from previous risk factors present in the civilian population and those unique to a theater of war (e.g., explosive mechanism of injury and theater of operation) [6,12–15]. Continuous variables were reported as medians (with interquartile ranges the 25th and 75th percentiles) and compared using Student *t* test or Mann–Whitney test, whichever is most appropriate. Categorical variables were reported as numbers and percentages and were compared using χ^2 test. In defining independent risk factors for VTE, significance was set at $P < 0.05$. Risk factors associated with PE were entered into a logistic regression model. Backward elimination was then applied so that only factors with P values <0.20 were included in the final model. A logistic regression model, followed by backward elimination was also used for amputee risk factor identification.

3. Results

From September 2001 through July 2011, there were 26,634 subjects available for analysis; 587 subjects (2.2%) developed a VTE (Fig. 1). Of these, there were 270 subjects (1.0%) with DVT, 223 (0.8%) with PE, and 94 (0.4%) with both DVT and PE. Of those who developed VTE, 12% were identified in theater, whereas 36% and 52% were identified at level IV (LRMC) and level V tertiary care centers in the United States, respectively. Overall, a higher percentage of casualties who developed VTE had an ISS >10, were injured with an improvised explosive device (IED), or suffered a penetrating injury (Table 1). After univariate analysis (Table 2), risk factors associated with PE included injury in OIF and blunt mechanism of injury. Of these subjects with a PE, 3.5% died. During multivariate analysis, the only independent risk factor for PE was lower extremity amputation (Table 3).

A total of 1003 of 26,634 combat casualties (3.7%) suffered lower extremity amputations; 174 (17.3%) of these subjects with lower extremity amputations developed VTEs (Fig. 1).

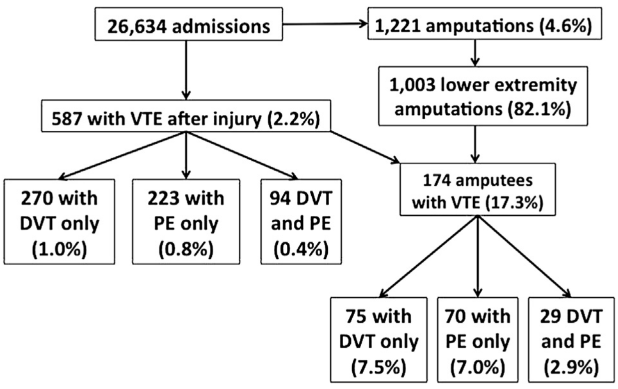

Fig. 1 – VTE consort diagram.

Table 1 – Demographics.

Variables	All casualties	VTE population	All amputees	Amputation and VTE
Age	24 (21 29)	25 (22 30)	23 (18 46)	25 (22 29)
Male	96.6%	98%	98%	99%
Army	74.5%	81%	68%	73%
ISS	5 (2 8)	22 (14 30)	18 (1 75)	24 (18 33)
ISS < 10	72%	8%	9%	2%
10 ≤ ISS < 25	20%	50%	66%	54%
ISS ≥ 25	8%	42%	25%	44%
Extremity AIS ≥3	17%	79%	94%	99%
Mechanism				
Gun shot wound	14%	18%	4%	2%
IED	49%	70%	93%	95%
Motor Vehicle Crash	8%	6%	2%	1%
Other	29%	6%	1%	2%
Injury				
Blunt	56%	45%	24%	37%
Penetrating	37%	55%	76%	63%

Median: 25th 75th percentiles.

Of the risk factors analyzed, eight (injury in OEF, multiple amputations, above the knee amputation, blunt mechanism, increased ISS, higher head and neck AIS, higher abdomen AIS, and higher extremity AIS) were associated with VTE on univariate analysis with $P < 0.05$ for all factors (Table 2). Multiple logistic regression identified OEF, penetrating injury, multiple amputations, and transfemoral amputation as independent risk factors for the development of VTE complications (Table 3).

Of 174 amputees with a VTE, 99 subjects (56.8%) were diagnosed with a PE (Fig. 1). Risk factors associated with the development of PE in amputees were an injury in OEF, blunt mechanism, multiple amputations, transfemoral amputation, and higher ISS, specifically an increased abdomen and extremity AIS (all $P < 0.05$; Table 2). After multiple logistic regressions, the independent risk factors for developing a VTE included OEF, blunt mechanism, multiple amputations, and transfemoral amputation (Table 3).

4. Discussion

VTE occurs in 2.2% of combat casualties, where 1% of all combat casualties developed a DVT, 0.8% a PE and 0.4% both DVT and PE. The distribution of VTE subtypes from our study was 46% DVT, 38% PE, and 16% concomitant DVT and PE. In combat casualties with VTE, amputation was the only risk factor associated with developing a PE (odds ratio, 1.70; 95% CI, 1.07–2.69). In the amputee population, the incidences of DVT, PE, and both DVT and PE were 7.5%, 7.0%, and 2.8%, respectively. Here, the risk factors of multiple amputations and a transfemoral amputation increased the likelihood of a VTE by more than 1.5 times.

To date, the best estimates of incidence of VTE in the trauma population come from large trauma database studies. In 2004, a study was released by Knudson *et al.*, who queried the American College of Surgeon's National Trauma Data Bank for episodes of DVT and PE in the U.S. civilian trauma population. From a total of 450,375 patients, Knudson *et al.* [13] reported that 0.36% had a VTE, 0.22% had a DVT, 0.12% had a PE, and 0.02% had both DVT and PE. This study also identified six risk factors independently associated with VTE in the civilian population which include age ≥40, both lower extremity fracture and AIS head ≥3, ventilator days >3, venous injury, and a major operative procedure.

In a separate study of more than 73,000 high risk trauma patients (i.e., those with one or more of the following: pelvic fracture, lower extremity fracture, severe closed head injury, and spinal cord injury), Stawicki *et al.* [15] found that the overall incidence of DVT was 1.9% or 2.2% if only level 1 trauma centers were included, with an overall incidence of PE at 0.5%. The authors observed that the lowest incidence of DVT was with isolated lower extremity fracture (1.3%), whereas the highest incidence was for combined pelvic fracture, lower extremity fracture, and closed head injury (5.4%). Although preexisting conditions and age were associated with VTE, the only variable in this study predictive of VTE was ISS.

Paffrath *et al.* [16] similarly screened the Trauma Registry of the German Society of Trauma Surgery for all clinically relevant VTEs. From 35,000 trauma patients reviewed, the overall frequency of VTE reported was 1.8%, with 49% developing DVTs, 37% developing PEs, and 14% developing both DVTs and PEs; these data are consistent with our results and that of the study by Knudson *et al.* In the German trauma registry study, the independent risk factors associated with VTE include ISS, number of operative procedures, the presence of a pelvic AIS ≥2, and concomitant disease(s). The authors considered only those subjects with a "relevant trauma load" to be ISS ≥9, which may explain the higher incidence of VTE in this and the study by Stawicki *et al.*, when compared with other studies performed across all ISS. Finally, the authors report that more than 80% of all subjects who developed a VTE in this study were on either mechanical or chemical prophylaxis.

Our study shows a similar incidence of VTE in service members injured during combat when compared with a civilian trauma cohort with comparable ISS, such as the latter two studies. However, in a recent study by Holley *et al.*, which is a subset of our study population who were evacuated

Table 2 – Risk factors associated with PE and VTE (univariate analysis).

Variables analyzed	Casualties with PE	Amputees with VTE	Amputees with PE
Death	OIF	OEF	OEF
Male	Blunt injury	Blunt injury	Blunt injury
Army		Multiple amputations	Multiple amputations
Battle injury		Transfemoral amputation	Transfemoral amputation
OIF		ISS	ISS
Explosive device		Head and neck AIS	Abdomen AIS
Penetrating injury		Abdomen AIS	Extremity AIS
Blunt injury		Extremity AIS	
Compartment syndrome			
Pelvic fracture			
Spinal cord injury			
Ankle/foot fracture			
Tibia/fibula fracture			
Femur fracture			
Venous injury			
Lower extremity amputation			
Multiple amputations			
Transfemoral amputation			
ISS			
Head and neck AIS			
Face AIS			
Chest AIS			
Abdomen AIS			
Extremity AIS			
Vital signs			
Initial heart rate			
Initial Systolic Blood Pressure			
Initial Diastolic Blood Pressure			
Initial SaO_2			
Initial Glasgow Coma Scale			
Initial pH			
Initial $PaCO_2$			
Initial PaO_2			
Initial base deficit			
Initial International Normalized Ratio			
Initial platelet count			

All $P < 0.20$ are included in the multivariate analysis.

to level V care at Walter Reed Medical Center between September 2009 and March 2011, the incidence of VTE during evacuation was 3.6% but increased to 5.5% during the hospital stay [17]. The increased rate of traumatic amputations during the Holley *et al.* study period may account for the difference in incidence of VTE in combat wounded when compared with the present study (Fig. 2) [14]. Risk factors for VTE are also different between ours and this later study, in that we show lower extremity amputation as the only risk factor predictive of VTE, with an incidence of 17% in this population, whereas Holley *et al.* showed that the transfusion of packed red blood cells was associated with an increased risk, both being markers of severe injury. Furthermore, the differences in risk factors between the military and civilian populations may be, in part, because of the contrasting demographic variables collected between studies and the prevailing mechanisms of injury. When comparing a civilian cohort with combat casualties, combat wounded tend to be a younger, more homogenous population who are severely injured. In addition, combat casualties are more likely to be injured by IEDs, and thus prone to traumatic amputations. In fact, 70% of our study population and 65% of the study by Holley *et al.* were injured with IEDs, a mechanism of injury rarely seen in civilian trauma, and this may account for the higher incidence of VTEs in this population [17].

In this present study, the incidence of PE was 1.2% but increased to 10% in the presence of a lower extremity amputation. Similar to our results, Gillern *et al.* studied combat casualties with wartime extremity wounds admitted to the National Naval Medical Center (level V) between March 2004 and December 2007, which overlaps our study period and population, and found that lower extremity trauma associated amputation had a higher incidence of PE than those with lower extremity long bone fracture without amputation; likewise, bilateral lower extremity trauma associated amputations were also associated with a higher incidence of PE when compared with those with a single amputation [18].

Because combat wounded, especially those with traumatic amputations, are at high risk for developing VTE, providers in theater should administer appropriate VTE prophylaxis as soon as the acute coagulopathy is corrected and the patient is not otherwise at increased risk of bleeding as is currently recommended in the Joint Theater System Clinical Practice

Table 3 – Risk factors (multivariate analysis).

Variable	Odds ratio	95% CI	P value
Independent risk factors for PE in all casualties			
Blunt injury	1.59	1.01 2.56	0.05
Spinal cord injury	0.44	0.17 1.14	0.09
Amputation	1.7	1.07 2.69	**0.03**
Initial SaO_2	1.03	0.99 1.06	0.12
Independent risk factors for VTE in amputees (multivariate analysis)			
OEF	2.94	1.75 5.00	**< 0.0001**
Penetrating	3.23	1.89 5.56	**< 0.0001**
Multiple amputations	2.15	1.35 3.42	**0.0013**
Above knee amputation	2.11	1.34 3.32	**0.0014**
Independent risk factors for PE in amputees (multivariate analysis)			
OEF	2.08	1.19 3.70	**0.0098**
Blunt injury	2.33	0.78 4.17	**0.0052**
Multiple amputations	1.67	1.00 2.78	**0.0482**
Above knee amputation	1.73	1.05 2.86	**0.033**

Bold entries are significant since they are less than specified P of 0.05.

Guideline [19]. In fact, Holley *et al*. showed that when enoxaparin is administered for most of the hospital days, the risk of VTE in this population is reduced [17]. Data regarding the use of DVT prophylaxis over the period of the study, especially during the time the combat casualty spends at levels III and IV, is either unavailable or incomplete. However, almost all patients who can safely receive DVT prophylaxis (i.e., enoxaparin or unfractionated heparin) have it administered at level IV (LRMC) often within 72 h of injury as per LRMC's Intensive Care Unit and ward DVT prophylaxis checklist; and those for whom it is contraindicated often receive retrievable inferior vena cava filters (LTC David Zonies, MD, MPH, FACS, USAF, personal communication, March 8, 2013). With this information regarding the practice of DVT prophylaxis in our population, which is similar to that reported by Paffrath *et al.* [16] and Gillern *et al*. [18], it appears that combat casualties are developing VTEs at a high rate despite adequate prophylaxis, which may be in part because of the large number of traumatic lower extremity amputations recorded in our dataset.

This study has several limitations: first, it possesses the inherent limitations of retrospective database review restricted to data available and collected during the study period and to a database not recorded in 'real time.' Hence, there may be subjects injured during the study period not yet entered into the DoDTR database. Second, our study does not include those casualties without VTE for comparison. Third, during the study period, we assume that all VTEs recorded were clinically significant in hospital events and no observational measures, such as surveillance Duplex imaging, were regularly practiced; therefore, the incidence of VTEs, especially silent DVTs, is likely higher. Fourth, this study extends over 10 y of war with data collected from combat casualties wounded in two disparate theaters of operation; therefore, changing injury patterns and clinical practice may have affected some study variables. Last, the DoDTR database includes U.S. troops treated in U.S. facilities; those U.S. troops treated at coalition facilities in theater may not be included in this study.

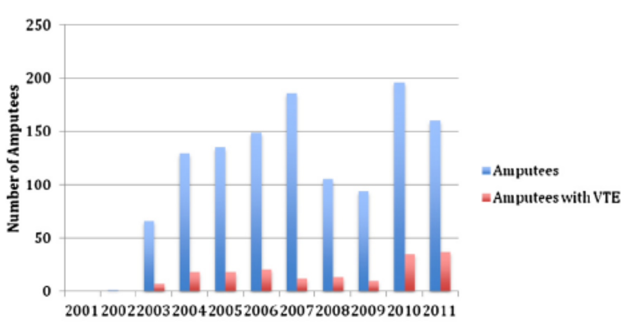

Fig. 2 – Amputee injury dates. (Color version of figure is available online.)

5. Conclusions

VTE occurs up to six times more frequently in combat casualties than in the civilian trauma population. In our population of military wounded, the risk of developing a PE is 70% higher with a lower extremity amputation and increases with higher or bilateral amputation. Combat casualties, and specifically lower extremity amputees, are highly susceptible to VTEs. Providers must have a heightened awareness for prevention, detection, and treatment of VTEs in this population, especially in those who have suffered lower extremity amputations.

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